

SEQUENCE LISTING

<110> Wyeth
WOLFMAN, Neil
TOMKINSON, Kathy

<120> METALLOPROTEASE ACTIVATION OF MYOSTATIN, AND METHODS OF MODULATING
MYOSTATIN ACTIVITY

<130> 08702.0128-00000

<150> US 60/486,863
<151> 2003-07-10

<150> US 60/439,164
<151> 2003-01-09

<150> US 60/411,133
<151> 2002-09-16

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<170> PatentIn version 3.1

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Lys Ser Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys Leu				
cgt ctg gaa aca gct cct aac atc agc aaa gat gtt ata aga caa ctt	65	70	75	298
Arg Leu Glu Thr Ala Pro Asn Ile Ser Lys Asp Val Ile Arg Gln Leu				
tta ccc aaa gct cct cca ctc cgg gaa ctg att gat cag tat gat gtc	85	90	95	346
Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val				
cag agg gat gac agc agc gat ggc tct ttg gaa gat gac gat tat cac	100	105	110	394
Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His				
gct aca acg gaa aca atc att acc atg cct aca gag tct gat ttt cta	115	120	125	442
Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe Leu				
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aaa ctt gac atg aac cca ggc act ggt att tgg cag agc att gat gtg	195	200	205	682
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Arg	Leu	Glu	Thr	Ala	Pro	Asn	Ile	Ser	Lys	Asp	Val	Ile	Arg	Gln	Leu
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 195 200 205

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 210 215 220

Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val Thr
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Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Lys
 245 250 255

Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys
 260 265 270

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 275 280 285

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Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala
 325 330 335

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 35 40 45

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cgc ctg gaa aca gct cct aac atc agc aaa gat gct atc aga caa ctt 240
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Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys			
260	265	270	
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275	280	285	
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Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala			

325

330

335

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 35 40 45

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Leu Pro Lys Ala Pro Pro Leu Leu Glu Leu Ile Asp Gln Phe Asp Val
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Ala Arg Thr Glu Thr Val Ile Thr Met Pro Thr Glu Ser Asp Leu Leu

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120

125

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Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu Gly
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Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
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Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys
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Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala
 325 330 335

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 35 40 45

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Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Arg			
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Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys			
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Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val			
275	280	285	

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 Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala
 325 330 335

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 340 345 350

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Lys Ser Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys Leu
 50 55 60

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	85							90						95	
Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His															
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Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe Leu															
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Val Gln Met Glu Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser Ser															
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Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser Leu															
	180				185			190							
Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp Val															
	195			200			205								
Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu Gly															
	210			215			220								
Ile Glu Ile Lys Ala Phe Asp Glu Thr Gly Arg Asp Leu Ala Val Thr															
	225			230			235			240					
Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Arg															
	245				250			255							
Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys															
	260			265			270								
Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val															
	275			280			285								
Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr															
	290			295			300								

Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys

305 310 315 320

Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala

325 330 335

Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr

340 345 350

Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ala Met Val

355 360 365

Val Asp Arg Cys Gly Cys Ser

370 375

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<211> 1125

<212> DNA

<213> Danio rerio

<220>

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<222> (1)..(1122)

<223>

<400> 7

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Met His Phe Thr Gln Val Leu Ile Ser Leu Ser Val Leu Ile Ala Cys

1 5 10 15

ggt cca gtg ggt tat gga gat ata acg gcg cac cag cag cct tcc aca 96

Gly Pro Val Gly Tyr Asp Ile Thr Ala His Gln Gln Pro Ser Thr

20 25 30

gcc acg gag gaa agc gag ctg tgt tcc aca tgt gag ttc aga caa cac

144

Ala Thr Glu Glu Ser Glu Leu Cys Ser Thr Cys Glu Phe Arg Gln His

35 40 45

agc aag ctg atg aga ctg cat gcc atc aag tcc caa att ctt agc aaa

192

Ser Lys Leu Met Arg Leu His Ala Ile Lys Ser Gln Ile Leu Ser Lys

50 55 60

ctc cga ctc aag cag gct cca aac atc agc cgg gac gtg gtc aag cag

240

Leu Arg Leu Lys Gln Ala Pro Asn Ile Ser Arg Asp Val Val Lys Gln

15

65

70

75

80

ctg tta ccc aaa gca ccg cct ttg caa caa ctt ctg gat cag tac gat 288
 Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln Leu Leu Asp Gln Tyr Asp
 85 90 95

gtt tta gga gat gac agt aag gat gga gct gtg gaa gag gac gat gaa 336
 Val Leu Gly Asp Asp Ser Lys Asp Gly Ala Val Glu Glu Asp Asp Glu
 100 105 110

cat gcc acc aca gag acc atc atg acc atg gcc aca gaa cct gac ccc 384
 His Ala Thr Thr Glu Thr Ile Met Thr Met Ala Thr Glu Pro Asp Pro
 115 120 125

att gtt caa gta gat cgg aaa ccg aag tgt tgc ttt ttc tcc ttc agt 432
 Ile Val Gln Val Asp Arg Lys Pro Lys Cys Cys Phe Phe Ser Phe Ser
 130 135 140

ccg aag atc caa gcg aac ccg atc gta aga gcg cag ctc tgg gtt cat 480
 Pro Lys Ile Gln Ala Asn Arg Ile Val Arg Ala Gln Leu Trp Val His
 145 150 155 160

ctg aga ccg gcg gag gag gcg acc acc gtc ttc tta cag ata tct ccg 528
 Leu Arg Pro Ala Glu Glu Ala Thr Thr Val Phe Leu Gln Ile Ser Arg
 165 170 175

ctg atg ccc gtt aag gac gga gga aga cac cga ata cga tcc ctg aaa 576
 Leu Met Pro Val Lys Asp Gly Gly Arg His Arg Ile Arg Ser Leu Lys
 180 185 190

atc gac gtg aac gca gga gtc acg tct tgg cag agt ata gac gta aag 624
 Ile Asp Val Asn Ala Gly Val Thr Ser Trp Gln Ser Ile Asp Val Lys
 195 200 205

cag gtg ctc acg gtg tgg tta aaa caa ccg gag acc aac cga ggc atc 672
 Gln Val Leu Thr Val Trp Leu Lys Gln Pro Glu Thr Asn Arg Gly Ile
 210 215 220

gag att aac gca tat gac gcg aag gga aac gac ttg gcc gtc act tca 720
 Glu Ile Asn Ala Tyr Asp Ala Lys Gly Asn Asp Leu Ala Val Thr Ser
 225 230 235 240

acc gag act ggg gag gat gga ctg ctc ccc ttt atg gag gtg aaa ata 768
 Thr Glu Thr Gly Glu Asp Gly Leu Leu Pro Phe Met Glu Val Lys Ile
 245 250 255

tca gag ggc cca aaa cga atc cgg agg gac tcc gga ctg gac tgc gat 816
 Ser Glu Gly Pro Lys Arg Ile Arg Arg Asp Ser Gly Leu Asp Cys Asp
 260 265 270

gag aat tcc tca gag tct cgc tgc tgc agg tac cct ctc act gtg gac 864
 Glu Asn Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val Asp
 275 280 285

ttc gag gac ttt ggc tgg gac tgg att att gct cca aaa cgc tat aag 912
 Phe Glu Asp Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr Lys
 290 295 300

gcg aat tac tgt tca gga gaa tgc gac tac atg tac ctg cag aag tat 960
 Ala Asn Tyr Cys Ser Gly Glu Cys Asp Tyr Met Tyr Leu Gln Lys Tyr
 305 310 315 320

ccc cac acc cat ctg gtg aac aag gcc agt ccg aga gga acg gct ggg 1008
 Pro His Thr His Leu Val Asn Lys Ala Ser Pro Arg Gly Thr Ala Gly
 325 330 335

ccc tgc tgc act ccc acc aag atg tct ccc atc aac atg ctt tac ttt 1056
 Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr Phe
 340 345 350

aac ggc aaa gag cag atc atc tac ggc aag atc cct tcg atg gta gta 1104
 Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ser Met Val Val
 355 360 365

gac cgc tgt ggc tgc tca tga 1125
 Asp Arg Cys Gly Cys Ser
 370

<210> 8
 <211> 374
 <212> PRT
 <213> Danio rerio

<400> 8

Met His Phe Thr Gln Val Leu Ile Ser Leu Ser Val Leu Ile Ala Cys
 1 5 10 15

Gly Pro Val Gly Tyr Gly Asp Ile Thr Ala His Gln Gln Pro Ser Thr

20

25

30

Ala Thr Glu Glu Ser Glu Leu Cys Ser Thr Cys Glu Phe Arg Gln His
 35 40 45

Ser Lys Leu Met Arg Leu His Ala Ile Lys Ser Gln Ile Leu Ser Lys
 50 55 60

Leu Arg Leu Lys Gln Ala Pro Asn Ile Ser Arg Asp Val Val Lys Gln
 65 70 75 80

Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln Leu Leu Asp Gln Tyr Asp
 85 90 95

Val Leu Gly Asp Asp Ser Lys Asp Gly Ala Val Glu Glu Asp Asp Glu
 100 105 110

His Ala Thr Thr Glu Thr Ile Met Thr Met Ala Thr Glu Pro Asp Pro
 115 120 125

Ile Val Gln Val Asp Arg Lys Pro Lys Cys Cys Phe Phe Ser Phe Ser
 130 135 140

Pro Lys Ile Gln Ala Asn Arg Ile Val Arg Ala Gln Leu Trp Val His
 145 150 155 160

Leu Arg Pro Ala Glu Glu Ala Thr Thr Val Phe Leu Gln Ile Ser Arg
 165 170 175

Leu Met Pro Val Lys Asp Gly Gly Arg His Arg Ile Arg Ser Leu Lys
 180 185 190

Ile Asp Val Asn Ala Gly Val Thr Ser Trp Gln Ser Ile Asp Val Lys
 195 200 205

Gln Val Leu Thr Val Trp Leu Lys Gln Pro Glu Thr Asn Arg Gly Ile
 210 215 220

Glu Ile Asn Ala Tyr Asp Ala Lys Gly Asn Asp Leu Ala Val Thr Ser
 225 230 235 240

Thr Glu Thr Gly Glu Asp Gly Leu Leu Pro Phe Met Glu Val Lys Ile
 245 250 255

Ser Glu Gly Pro Lys Arg Ile Arg Arg Asp Ser Gly Leu Asp Cys Asp
 260 265 270

Glu Asn Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val Asp
 275 280 285

Phe Glu Asp Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr Lys
 290 295 300

Ala Asn Tyr Cys Ser Gly Glu Cys Asp Tyr Met Tyr Leu Gln Lys Tyr
 305 310 315 320

Pro His Thr His Leu Val Asn Lys Ala Ser Pro Arg Gly Thr Ala Gly
 325 330 335

Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr Phe
 340 345 350

Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ser Met Val Val
 355 360 365

Asp Arg Cys Gly Cys Ser
 370

<210> 9
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 9

Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu
 1 5 10 15

Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly Ser
 20 25 30

Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met
 35 40 45

Pro Thr
 50

<210> 10
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Mutant peptide portion of human myostatin

<400> 10

Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu
1 5 10 15

Leu Ile Asp Gln Tyr Asp Val Gln Gln Asp Asp Ser Ser Asp Gly Ser
20 25 30

Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met
35 40 45

Pro Thr
50

<210> 11
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Mutant peptide portion of human myostatin

<400> 11

Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu
1 5 10 15

Leu Ile Asp Gln Tyr Asp Val Gln Arg Ala Asp Ser Ser Asp Gly Ser
20 25 30

Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met
35 40 45
Pro Thr
50

<210> 12
<211> 40
<212> PRT
<213> Homo sapiens

<400> 12

Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr
1 5 10 15

Asp Val Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp
20 25 30

Tyr His Ala Thr Thr Glu Thr Ile
35 40

<210> 13
<211> 40
<212> PRT
<213> Artificial sequence

<220>
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<400> 13

Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr
1 5 10 15

Asp Val Gln Gln Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp
20 25 30

Tyr His Ala Thr Thr Glu Thr Ile
35 40

<210> 14
<211> 40
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<220>

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<400> 14

Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr
 1 5 10 15

Asp Val Gln Arg Ala Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp
 20 25 30

Tyr His Ala Thr Thr Glu Thr Ile

35 40

<210> 15

<211> 30

<212> PRT

<213> Homo sapiens

<400> 15

Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp
 1 5 10 15

Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His Ala
 20 25 30

<210> 16

<211> 30

<212> PRT

<213> Artificial sequence

<220>

<223> Mutant peptide portion of human myostatin

<400> 16

Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val Gln Gln Asp
 1 5 10 15

Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His Ala
 20 25 30

<210> 17
<211> 30
<212> PRT
<213> Artificial sequence

<220>
<223> Mutant peptide portion of human myostatin

<400> 17

Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Ala
1 5 10 15

Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His Ala
20 25 30

<210> 18
<211> 20
<212> PRT
<213> Homo sapiens

<400> 18

Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly
1 5 10 15

Ser Leu Glu Asp
20

<210> 19
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Mutant peptide portion of human myostatin

<400> 19

Glu Leu Ile Asp Gln Tyr Asp Val Gln Gln Asp Asp Ser Ser Asp Gly
1 5 10 15

Ser Leu Glu Asp

20

<210> 20
<211> 20
<212> PRT
<213> Artificial sequence

<220>
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<400> 20

Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Ala Asp Ser Ser Asp Gly
1 5 10 15

Ser Leu Glu Asp
20

<210> 21
<211> 10
<212> PRT
<213> Homo sapiens

<400> 21

Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp
1 5 10

<210> 22
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<400> 22

Tyr Asp Val Gln Gln Asp Asp Ser Ser Asp
1 5 10

<210> 23
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<400> 23

Tyr Asp Val Gln Arg Ala Asp Ser Ser Asp
1 5 10